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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,827	ROSEN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-64 is/are pending in the application.

4a) Of the above claim(s) 1-19,21,22,24,26-30,32,34-48,58 and 60-63 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 20, 23, 25, 31, 33, 49-57, 59, 64 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/17/04;11/7/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filled Oct. 24, 2005 is acknowledged. The traversal is on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of other groups such as I-III, V and VI necessarily represents an undue burden for the examiner. Applicant argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group were found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition are rejoined for the examination purposes. Applicant's argument of examining other compositions and method of treatment with other composition (group I-III and V) with elected group is not persuasive because examination of the invention of different method and or composition groups would require undue search burden for reasons of record set forth in the previous office action of page 3 lines 17-26. Furthermore, examining a composition and method of using that composition is only one limitation and Examiner has to consider the method steps for other groups and perform searches. For example, composition and method of treating cardiac disorder using composition comprising stem cell modified with a nucleic acid will be distinct and different compare to stem cell modified with a small molecule or a compound. Thus, require separate search and these searches would be undue burden since compositions and method of treatment using these distinct compositions would have to considered. Additionally, the

different inventions have different status in the art because they are drawn to different structure and functions.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, a composition for ion channel transfer, which comprises stem cells, incorporated with a compound in an amount sufficient to create ion channel and method to express ion channel and treatment of cardiac condition will be examined in the instant application.

2. Groups I-III and V (claims 1-19, 21, 22, 24, 26, 27-30, 32, 34-38, 39-48, 58 and 60-63) have been have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 24, 2005.

3. Claims 20, 23, 25, 31, 33, 49-57, 59 and 64 are under consideration.

It is noted that the claims 49-57, 59 and 64 of groups IV and VI are included in multiple groups because they encompass the inventions of these groups. However these claims will be examined to the extent it encompass the invention of the elected group, a composition for ion channel transfer, which comprises stem cells, incorporated with a compound in an amount sufficient to create ion channel and method to express ion channel and treating cardiac condition using said composition.

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Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 49, 50, 54 and 55 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recite the limitation "cardiac rhythm disorder" in the claim, which depends on claim 51 drawn to a method of treating cardiac condition. There is insufficient antecedent basis for this limitation in the claim.

Claim 55 recite the limitation "structure" in the claim, which depends on claim 51 drawn to a method of treating cardiac condition. There is insufficient antecedent basis for this limitation in the claim.

Claims 49 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Preparation of stem cell comprising compound that expresses ion channel in amount sufficient such that it expresses ion channel and then microinjecting said cell into anterior wall of the heart such that said cell gets engrafted with in the heart. Claim 50 is dependent on claim 49.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49- 57 and 59 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention recite a method of expressing a functional ion channel in a syncytial structure comprising a stem cell incorporated with compound in quantity sufficient to express ion channel in heart. Subsequent claims recite a method of treating a cardiac condition in any subject, which comprises contacting a cell of heart with the stem cell incorporated with a compound in an amount sufficient to increase the pacemaker current for the treatment of cardiac condition. The claims are also drawn to a method of inducing current in the heart of any subject by delivering the stem cell incorporated with the compound that express ion channel. The invention also encompasses a method of inducing current in a cell which comprises contacting a cell with the composition comprising a stem cell incorporated with compound that express ion channel.

The application as filed is not enabling because art of cell therapy in human with stem or genetically modified stem cell for the cardiac disorder was *unpredictable* as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, the broad aspects as well as limitations were not enabled for the claimed invention at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification,

therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised by the art by artisan of expertise.

The specification as filed provides a general description of pacemakers and cardioactive drugs and summary of inventions (pp 1-6). Page 7-9 describes brief description of figures showing transfer of Lucifer yellow dye from stem cell to HeLa cell and coupling and ionic dye transfer between stem cell and a canine cardiomyocyte. Page 10-18 provides a detailed description of the invention, preferred embodiments and definitions of terms. Page 19-34 discloses a proposal in five different phases that includes for expression, regulation of pacemaker gene *in vitro*, *in vivo*, and in isolated tissue.

The specification does not provide any specific guidance for the claimed invention because the specification as filed does not indicate whether engrafted cells are stem cells. In absence of any specific staining for gap junction, it is difficult to extrapolate that engrafted cells form gap junction with cardiac cells. Furthermore, specification does not disclose number of stem cell that are required to be engrafted in heart for pharmacological response for the treatment of any cardiac condition. The specification also does not give any correlation between number of stem cell delivered that are engrafted at the site of action to number of cells that are relocated to other places. The method of transplanting genetically modified stem cells in human was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

Specification's description of examples on pages 7-9 disclose the transfer of Lucifer yellow dye from stem cell to HeLa cells transfected with Cx43 showing transfer of dye by diffusion through gap junction. Figures 3(A-C) show coupling and ionic and dye transfer between stem cells and a canine cardiomyocyte while Figure 4(A-B) demonstrate stem cell coupling with HeLa cells. Figure 5, 6 and 8 show human mesenchymal stem cell and inward rectification, needle survival and transient transfection of MSC. Figure 8 and 9 disclose HCN2 incorporate stem cell could generate pacemaker current while Figure 10(A-E) demonstrate expression of pacemaker current in canine ventricle *in situ* as a result of implanting mesenchymal stem cell having the HCN2 pacemaker gene.

Claims 49-57 and 59 are directed to method of expressing ion channel in the syncytial structure and method of treating cardiac condition using a composition comprising stem cell incorporated with a compound that expresses ion channel. Although the specification shows the role and importance of implantation of stem cells incorporated with HCN2 gene in canine's heart for pacemaker activity, however, these disclosures do not demonstrate the information required by the Artisan to reasonably predict the optimal number stem cells that are required for pacemaker activity for the treatment of any cardiac condition as claimed in the instant application. Furthermore, specification does not provide any specific guidance of any correlation between the numbers of cells required for successful pacemaker activity for a sustained period. Furthermore, an artisan of skill would have to perform undue experimentation to ensure that HCN2 is stably expressed for a long duration in order to express ion channel gene

for a sustained pacemaker activity. In other words, the art did not teach and was unpredictable at the time of invention, as to how many stem cells and how much HCN2/ion channel expression is required for desired pharmacological response for appropriate period.

The claims 51-52, 57 and 59 read on treating any heart condition in a subject which comprises an *in vivo* method of delivering any stem cell incorporated with any compound and specification as filed does not provide sufficient guidance or factual evidence for one skilled in the art to practice the claimed methods. There are many cardiac conditions known in the art. The instant claims read on treating any cardiac condition (arthrosclerosis, restenosis, cardiac rhythm disorder, tachycardia, bradycardia etc.) in subject using the claimed method and claimed methods as filed does not disclose which conditions are treatable by the claimed method. Furthermore, cardiac conditions that are caused by defects in the conduction system that prevent electrical impulse reaching the ventricle would not be efficacious or treated by delivering stem cell incorporated with HCN2 gene. Zhang et al (Circulation, 2002; 106(10): 1294-9) describe that "totipotent stem cells may be the source of unanticipated arrhythmias after cell transplantation therapy by enhancing the likelihood of all three basic arrhythmic mechanisms. Zhang et al state "stem cell engraftment preferentially in areas of injury is likely to promote arrhythmic tendency which raises concern of stem cell that are differentiated to cardiac myocyte before engraftment in the heart" (pp1299; last paragraph). In fact even two year after filing of instant application Mocini et al, (Ital Heart J. 2005; 6(3): 267-71) disclose "concern exists about the possible occurrence of serious

arrhythmias after stem cell transplantation, even if such complication has been shown only in case of skeletal myoblast transplantation. Mocini et al describes "stem cell transplantation might induce arrhythmias by several mechanisms, such as electro-tonic stimulation of cardiac cells, electrical heterogeneity of action potentials during stem cell differentiation process, increased nerve sprouting, and local tissue injury induced by intra-myocardial injection". Mocini et al evinces an optimistic outlook on genetically modified mesenchymal stem cells that can be delivered within the heart and engraft to develop a biological pacemaker. However Mocini et al conclude "To date, several studies have been performed in different animal models employing both cell and gene therapy. However, Mocini et al emphasize that complex problems concerning safety and **efficacy** require a solution before clinical evaluation in **human** beings"(abstract).

The instant claims 51, 57 and 59 recite term current expression in a cell of the heart, which encompasses several type of current in the heart (eg. Potassium, sodium etc) and HCN2 is only associated with increasing expression of pacemaker current (Proenza et al., The Journal of Biological Chemistry, 277, 2002, 5101-5109). Thus, claimed methods are not enabled for inducing any other current in heart.

Next, despite the success of myoblast transplantation and its recent trial in human, the mechanism responsible for the functional improvement remains unclear. Leobon et al used intracellular recordings coupled to video and fluorescence microscopy to show that grafted myoblasts differentiate into peculiar hyperexcitable myotubes with a contractile activity fully independent of neighboring cardiomyocytes. Leobon et al conclude that mechanisms other than electromechanical coupling between

grafted and host cells are involved in the improvement of cardiac function (Leobon et al., Proc Natl Acad Sci U S A. 2003; 100(13): 7808-11). In addition, Leobon concluded that transplanted cells are functionally isolated from their host (pp 7811). Although, the studies by Leobon are not exactly, the same as claimed in instant application but they raise unpredictability in the art of electro-mechanical coupling of grafted cells. Furthermore neither the specification nor the art of record provide any specific guidance of potential altered biophysical and trans-differentiation of stem cell during prolonged expression of transgene in the heart that could have adverse impact on pacemaker activity.

It is not apparent as how skilled artisan could carry over these inventions in any subject without undue experimentation encompassing treating **any cardiac condition** in any subject. It is also not apparent how skilled artisan without any undue experimentation, practices method as contemplated by the instant claims particularly given the unpredictability of nucleic acid and cell therapy as whole and unpredictability expressed in the art.

It is noted, the specification is not enabling for practicing the claimed method of using any stem. The specification, does not disclose therapy guidance as to how would the method of ex vivo cell therapy would be carried out.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the

claimed inventions. The specification and prior art do not teach a method of administering genetically modified stem cell in humans. An artisan of skill would have required undue experimentation to practice the invention because the art of ex *vivo* gene delivery and cell therapy in general was unpredictable at the time of filling of this application as supported by the observations in the art record.

7. Claim 20, 23, 25, 31, 33, 49-57, 59 and 64 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claimed invention encompasses a genus of compound incorporated in any stem cell for ion channel transfer in a method of treating a genus of cardiac condition by inducing any current.

When claims are analyzed in light of the specification, instant invention encompasses any compound including small molecule, any cardiac condition and any type of current. In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not disclose a genus of small molecule incorporated in any stem cell that could induce current in any cardiac conditions. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims require more than mere statement that it is par of invention and reference to potential

method/or molecule that are essential for a genus of compounds used to treat a cardiac conditions claimed. The specification does not provide any disclosure as to what would have been the structure of the representative number of the species of the claimed broad genus as disclosed in specification.

Next, then it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification merely shows that sequence encoding HCN2 gene incorporated mesenchymal stem cell has potential to induce current when engrafted in canine heart. The specification does not teach the structure and identifying characteristics of a sufficient number of representative species of different **stem cells**, **small molecule**, HCN2 sequence of **other species**, **cardiac condition** or different type of **current**. The skilled artisan cannot envision the detailed structure of a genus of compounds or stem cell that must show the contemplated biological activity, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity/simplicity of the structure and/or methods disclosed in specification.

In conclusion, this limited information is not deemed sufficient to reasonably convey one skilled in art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed broad inventions.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 64 rejected under 35 U.S.C. 102(b) as being anticipated by Gerson et al., (US patent 5,591625, dated 01/07/1997; IDS).

Claim 64 is directed to a composition for delivery of small molecule that comprises **stem cell** incorporated with small molecule or **genes** encoding the small molecule.

Greson et al disclose isolated human mesenchymal stem cell transfected with exogenous genetic material encoding protein of interest (column 18, lines 43-46)

Accordingly, Greson et al. anticipate claims 64.

10. Claims 64 rejected under 35 U.S.C. 102(e) as being anticipated by Pittenger et al., (US patent 6,387,369, dated 05/14/2002, EFD 00/27/2000; IDS).

Claim 64 is directed to a composition for delivery of small molecule that comprises **stem cell** incorporated with small molecule or **genes** encoding the small molecule.

Pittenger et al teach a method of producing cardio-myocytes in vivo by administering to the heart **mesenchymal stem cell** that can be **genetically** modified to enhance myocardial differentiation and integration (abstract; column 6; line 8-21).

Accordingly, Pittenger et al. anticipate claims 64.

11. Claims 20, 23 and 25 rejected under 35 U.S.C. 102(e) as being anticipated by Marban et al (US Patent application Publication no. US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002).

Claim 20, 23, and 25 is drawn to a composition for ion channel transfer, which comprise **stem cells** incorporated with a compound in an amount sufficient to create **ion channel**. Subsequent claim limit the compound to be HCN2.

Marban et al disclose that composition of modified cells could be administered to induce or modulate pacemaker activity of cells or a subject. It is noted that source of modified cells are cardiac myocardial cells generated from differentiated **stem cells**, such as embryonic bone marrow cells. The stem-cell-derived cardiomyocytes exhibiting

pacemaker function then may be implanted such as by catheter or injection to targeted cardiac tissue (pp10, paragraph 121). Marban also teach genes that could be used to affect cardiac firing rate includes ion channels including HCN channels (pp6, paragraph 64). The teaching of Marban et al encompasses HCN2 channel as different isoform of HCN channel were known in the art and Marban et al intend to use HCN channels to affect firing rate of heart.

Accordingly, Marban et al. anticipate claims 20, 23 and 25.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 20, 23, 25, 27, 31, 33, and 64 rejected under 35 U.S.C. 103(a) as being unpatentable over Rosen et al (US patent no 6,849,611, effective filing date 06/06/2001) and in view of Heubach et al (Circulation, 106 (19) 2002, suppl. pp II-68).

Claim 20 is drawn to a composition for ion channel transfer, which comprise **stem cells** incorporated with a compound in an amount sufficient to create **ion channel**. Claims 23 and 25 limits the nucleic acid to a HCN channel, which is **HCN2** channel. Claims 31 and 33 limits the stem cells incorporated with a compound comprising nucleic acid that encodes **MiRP1 and a HCN2** channel. Claim 64 is directed

to a composition for delivery of small molecule that comprises **stem cell** incorporated with small molecule or **genes** encoding the small molecule.

Rosen et al teach regulation of pacemaker function of cardiac muscle cells in the heart with HCN molecules (HCN 1, 2, or 4 isoforms of the pacemaker) and/or MiRP1 beta subunit. These isoforms are shown to produce a functioning site of impulse initiation that serves as the initiator of a heartbeat by contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject (column 1 line 45-50). Figure 5 shows the activation relation and kinetics of I_{HCN2} expression with AdHCN2 in neonatal and adult ventricle. Rosen et al further teach a compound comprising a nucleic acid encoding HCN2 and MiRP1 in a sufficient amount to induce the pacemaker current in the cell of the heart of the subject, thereby inducing a pacemaker current in the cell of the heart of the subject suggesting that cell expresses sufficient ion channel to elicit an pharmacological response (column 22; claim 6). However, Rosen et al do not teach cell composition being stem cell or delivering mutant HCN2 gene.

Heubach et al disclose injection of autologous mesenchymal stem cell into the heart. Heubach characterized ion current and expression of 20 cardiac ion channels in human MSC obtained from bone marrow aspirate. Heubach concluded that undifferentiated MSC expresses a consistent pattern of ion channel mRNA and the outward current seen were likely to be carried by K+ channel.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the cells taught by Heubach et al by expressing a nucleic acid

encoding HCN2 taught by Rosen et al, for expressing ion channel genes in stem cell at sufficient level for pacemaker activity. Furthermore, Heubach et al had already shown that mesenchymal stem cell expresses consistent pattern of ion channel and could be directly administered to heart for novel cardiac therapy (abstract).

One who would practice the invention would have reasonable expectation of successfully producing a composition comprising stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed to different cardiac or stem cell for pacemaker activity. One of ordinary skill in art would have been motivated to combine the teaching of Rosen et al and Heubach et al because a composition comprising stem cell expressing HCN2 would have provided biological pacemaker activity and thus provide a novel cardiac therapy.

Therefore, the claimed invention would have been prima fascia obvious to one of ordinary skill in the art at the time of the invention.

14. No Claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where

this application or proceeding is assigned is 703-872-9306.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Anoop Singh, Ph.D.
Examiner, AU 1632